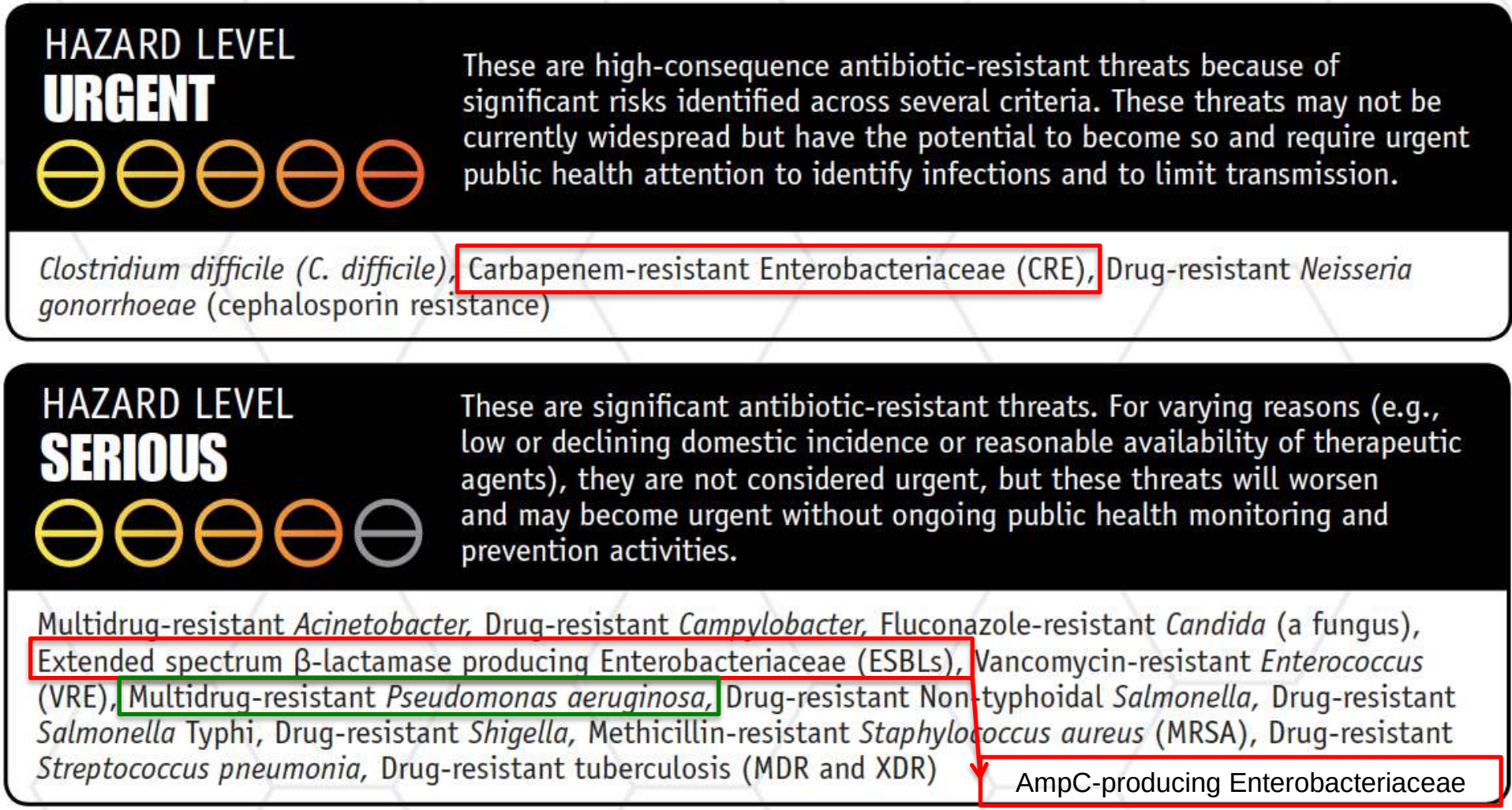
Treatment Strategies for MDR Gram-negative Infections in 2017

Michael Satlin, MD, MS
Assistant Professor of Medicine
Transplantation-Oncology Infectious Diseases Program
Division of Infectious Diseases
Weill Cornell Medicine

Disclosures

- I receive research grants/contracts from Allergan and Merck (through Weill Cornell Medicine)
- Member of CLSI Subcommittee on Antimicrobial Susceptibility Testing

CDC: Antibiotic Resistance Threats in the USA, 2013



Why 1st focus on MDR Enterobacteriaceae?

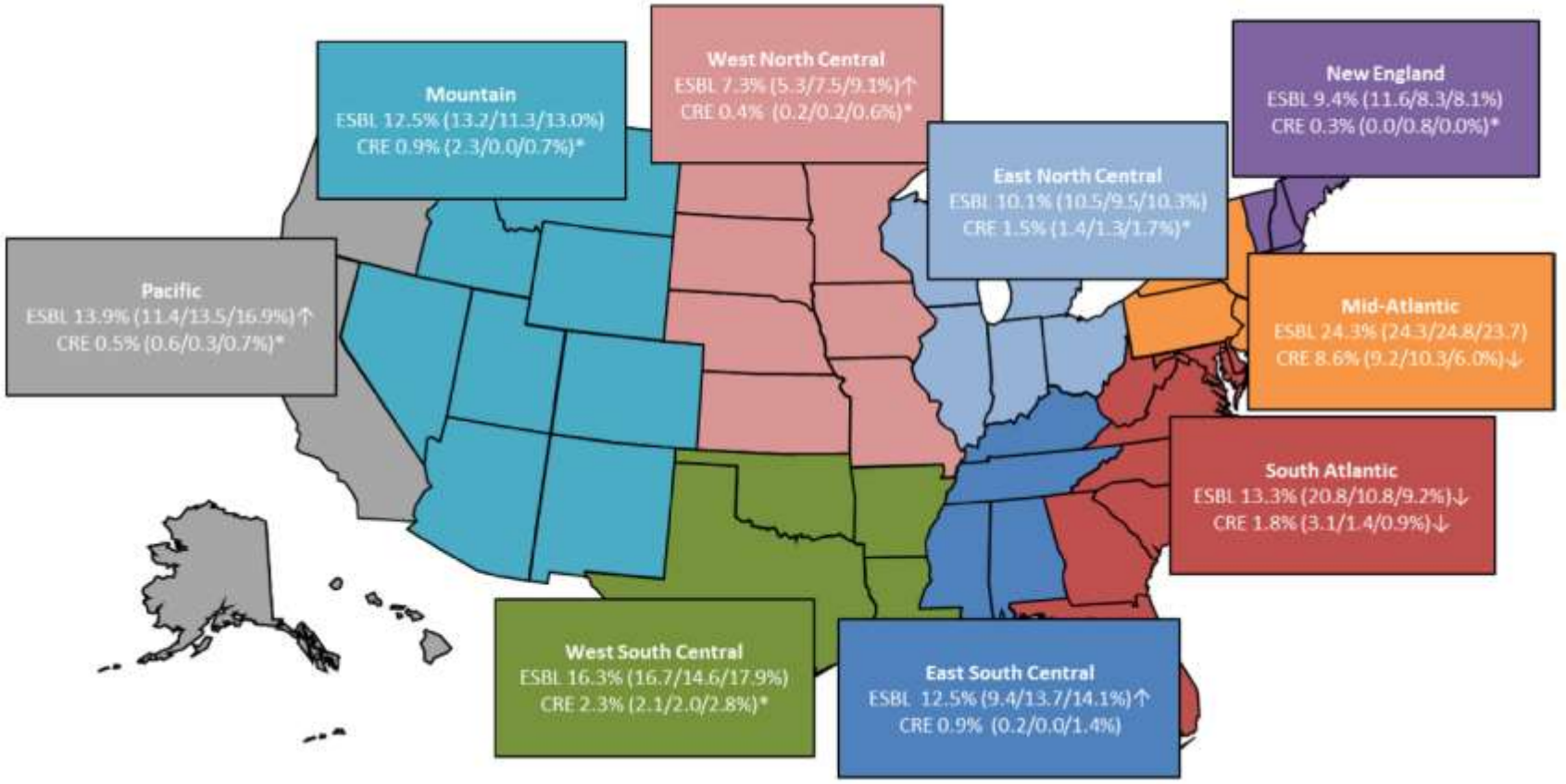
Data from a CDC HAI surveillance network in 2011-2014

Pathogen	Overall: No. (%) of pathogens	Overall: Rank[b]	Extended-spectrum **cephalosporin** resistance (%) CLABSI	**Carbapenem** resistance (%) CLABSI
Escherichia coli	62,904 (15.4)	1	22%	2%
Staphylococcus aureus	48,302 (11.8)	2		
Klebsiella (pneumoniae/oxytoca)	31,498 (7.7)	3	27%	12%
Coagulase-negative staphylococci[c]	31,361 (7.7)	4		
Enterococcus faecalis[d]	30,034 (7.4)	5		
Pseudomonas aeruginosa	29,636 (7.3)	6		
Candida albicans[d]	27,231 (6.7)	7		
Enterobacter spp[c]	17,235 (4.2)	8	37%	5%
Enterococcus faecium[d]	14,942 (3.7)	9		
Other *Enterococcus* spp.[d]	14,694 (3.6)	10		
Proteus spp.[c]	11,249 (2.8)	11		
Yeast NOS[e]	10,811 (2.6)	12		
Other *Candida* spp.[d]	10,641 (2.6)	13		
Candida glabrata[d]	8,121 (2.0)	14		
Bacteroides spp.	7,560 (1.9)	15		

Weiner LM, et al. Infect Control Hosp Epidemiol 2016.

Where are MDR Enterobacteriaceae?

63 hospitals: 2012-2014



Castanheira M, et al. Antimicrob Agents Chemother 2016.

Case #1

- 23 yo woman with T cell lymphoma underwent an allogeneic stem cell transplant. She was receiving levofloxacin prophylaxis and nine days after her stem cell infusion she developed **neutropenic fever** (up to 39.0°C) and tachycardia in the setting of mucositis and nausea. Blood cultures were collected and she was started on piperacillin-tazobactam. The blood cultures grew an ***E.coli*** with the following susceptibility pattern:

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Cefepime	8	S-DD	Meropenem	<=1	S
Cefoxitin	8	S	Piperacillin-tazobactam	<=8	S
Ceftazidime	>16	R	TMP-SMX	>2/38	R

- Her vital signs the morning these results return (2 days after bacteremia onset) are 37.9, HR 94, BP 96/60. She continues to have GI symptoms. She looks well, but is diaphoretic. The rest of her exam is normal. Her WBC count is < 0.1 cells/µL.

Case #1: Which antibiotic(s) would you choose to treat this bacteremia at this point?

A. Cefepime
B. Cefoxitin
C. Meropenem
D. Continue piperacillin-tazobactam

Ceftriaxone-resistant, carbapenem-susceptible Enterobacteriaceae: **ESBL vs. AmpC**

- How do you tell them apart?
- Does it matter?

Clue	**ESBL**	**AmpC**
Species	*Escherichia coli* *Klebsiella pneumoniae* *Klebsiella oxytoca* *Proteus mirabilis*	***S**erratia* ***P**rovidencia, Morganella* ***I**ndole-positive Proteus* ***C**itrobacter* ***E**nterobacter*
Cefoxitin	Susceptible	Resistant

ESBLs

- **CTX-M** is the dominant ESBL type in the USA (60-90%)[1-3]
  - **plasmid**-mediated
  - SHV and TEM ESBL types are much less common
- Susceptibility rates of CTX-M-producing Enterobacteriaceae[1-4]
  - Ceftazidime: 20-60%
  - Cefepime: 60-70%
  - Piperacillin-tazobactam: 70-95%
  - Carbapenems, cefoxitin, and ceftazidime-avibactam: 95-100%

- Should we always use carbapenems for these infections?

OR

- Can we use cefepime or pip-tazo if they test susceptible?

[1]Park SH, et al. Antimicrob Agents Chemother 2012.
[2]Castanheira M, et al. Antimicrob Agents Chemother 2014.
[3]Castanheira M, et al. Antimicrob Agents Chemother 2016.
[4]Guet-Revillet H, et al. Antimicrob Agents Chemother 2014.

ESBLs: Inoculum effect

- 10^5 CFU/mL is the standard inoculum for susceptibility testing
- What if you use 10^7 CFU/mL? (e.g., pneumonia)

Enzyme	Meropenem		Cefepime		Pip-tazo	
	10^5	10^7	10^5	10^7	10^5	10^7
SHV-2	0.03	0.03	8	>128	4	256
SHV-7	0.03	0.03	8	>128	2	64
TEM-43	0.03	0.06	1	32	2	4
TEM-12	0.03	0.06	4	>128	2	8
TEM-10	0.03	0.03	4	>128	2	2
TEM-4	0.03	0.03	4	>128	2	4
TEM-3	0.03	0.06	4	>128	2	4

[1]

- Similar findings have been shown for CTX-M ESBLs (*E. coli* and *K.pneumoniae*)[2,3]

[1]Thomson KS, et al. Antimicrob Agents Chemother 2001.
[2]Harada Y, et al. Clin Microbiol Infect 2014.
[3]Wu N, et al. Ann Clin Microbiol Antimicrob 2014.

ESBLs: Clinical Data

- No randomized studies comparing carbapenems to cefepime or pip-tazo, yet …
- Important problems with observational studies:
  - Confounding by indication
    - Sicker patients get carbapenems?
  - Distinction between
    - Empirical therapy: **initial** antibiotics given **before** susceptibility data available
    - Definitive therapy: antibiotics given **after** susceptibility data available

- Multivariate analysis
- Propensity score matching

Most important?

ESBLs: Clinical Data: Cefepime vs. Carbapenem

- 178 patients with ESBL-E bacteremias (*Ec, Kp*, others)

Empirical therapy	30-day mortality
Cefepime (cefepime-susceptible)	6/17 (35%)
Carbapenem	16/91 (18%)

Definitive therapy	Sepsis-related mortality
Cefepime	9/17 (53%)
Carbapenem (propensity score matched patients)	1/17 (6%)

Beware of cefepime for serious ceftriaxone-resistant *E.coli* or *Klebsiella* infections!

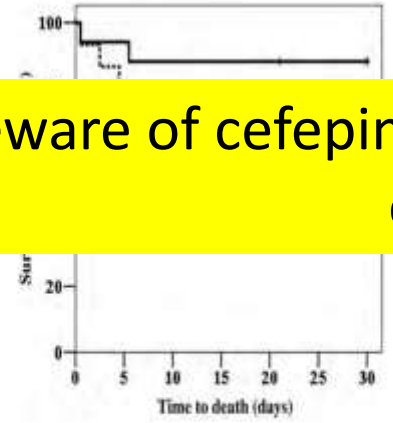


Figure 3. Kaplan-Meier survival analysis curves for patients with bacteremia caused by extended-spectrum ß-lactamase–producing organisms; bacteremia treated using a carbapenem (solid line) vs cefepime (broken line; log-rank test, $P = .016$).

Lee NY, et al. Clin Infect Dis 2013.

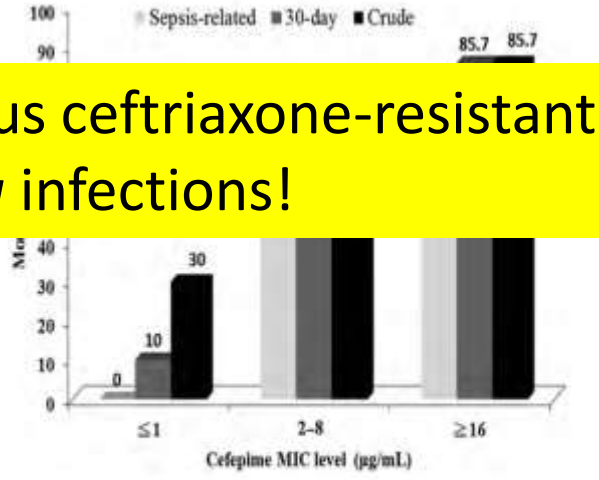


Figure 1. Mortality rates of 3 subgroups of patients who received cefepime therapy (n = 33) stratified by the cefepime minimum inhibitory concentration. Abbreviation: MIC, minimum inhibitory concentration.

Cefepime
Susceptible: Dose-dependent

Previous – 2013

Method	Susceptible	Intermediate	Resistant
MIC	≤8 μg/mL	16 μg/mL	≥32 μg/mL

Revised – 2014

Method	Susceptible	Susceptible-Dose Dependent	Resistant
MIC	≤2 μg/mL	4–8 μg/mL	≥16 μg/mL

Based on 1 g q12h dosing

Use 2 g q8h dosing

ESBLs: What about β-lactam-β-lactamase inhibitors (like piperacillin-tazobactam)?

- Post hoc analysis of patients with ESBL-*E.coli* bacteremia in 6 prospective cohorts
- Compared use of carbapenem or BL-BLI as monotherapy either empirically or as definitive therapy

	Empirical Therapy Cohort			Definitive Therapy Cohort		
Characteristic	BLBLI (n = 72)	Carbapenem (n = 31)	*P*	BLBLI (n = 54)	Carbapenem (n = 120)	*P*
Mortality, no. of deaths						
Day 7	2 (2.8)	3 (9.7)	.1[c]	1 (1.9)	5 (4.2)	.6[c]
Day 14	7 (9.7)	5 (16.1)	.3	3 (5.6)	14 (11.7)	.2
Day 30	7 (9.7)	6 (19.4)	.1	5 (9.3)	20 (16.7)	.1
Hospital stay after BSI , median (IQR), d	12 (8–28)	13 (9–25)	.7[b]	13 (8–22)	13 (10–25)	.04[b]

- No difference in mortality in multivariate analysis
- Notably: all ***E.coli***, mostly CTX-M, mostly bacteremias from **urinary or biliary** source, the highest dose of pip-tazo was used (**4.5 g every 6 h**), does not apply to ampicillin-sulbactam

Rodriguez-Baño J, et al. Clin Infect Dis 2012.

ESBLs: Clinical Data: Pip-tazo vs. Carbapenem

213 patients with ESBL bacteremia (*Ec*, *Kp*, *Proteus mirabilis*)
All received definitive treatment with a carbapenem
All isolates susceptible to pip-tazo and a carbapenem

Empirical therapy
1st 3 days

Pip-tazo (n=103)

Carbapenem (n=110)

14-day mortality 17% ← *P*=0.05 → 8%

Multivariate model
Adjusted HR of death 1.9 (1.1-3.5) if received pip-tazo empirically

- Only 40% received 4.5 g IV q6h
- Urine and biliary sources: only 25%
- Included *Klebsiella pneumoniae*

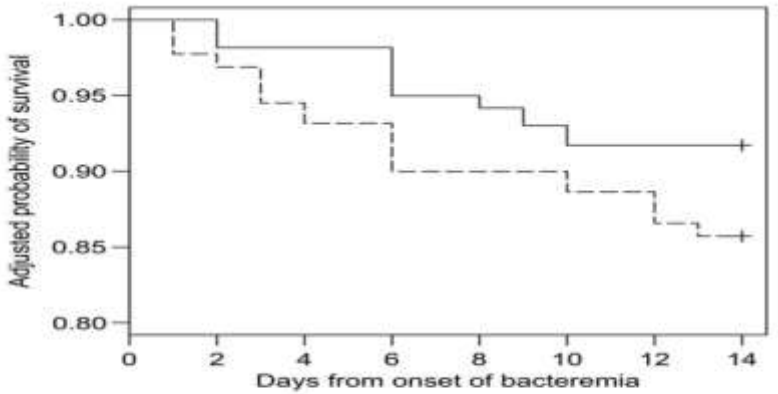


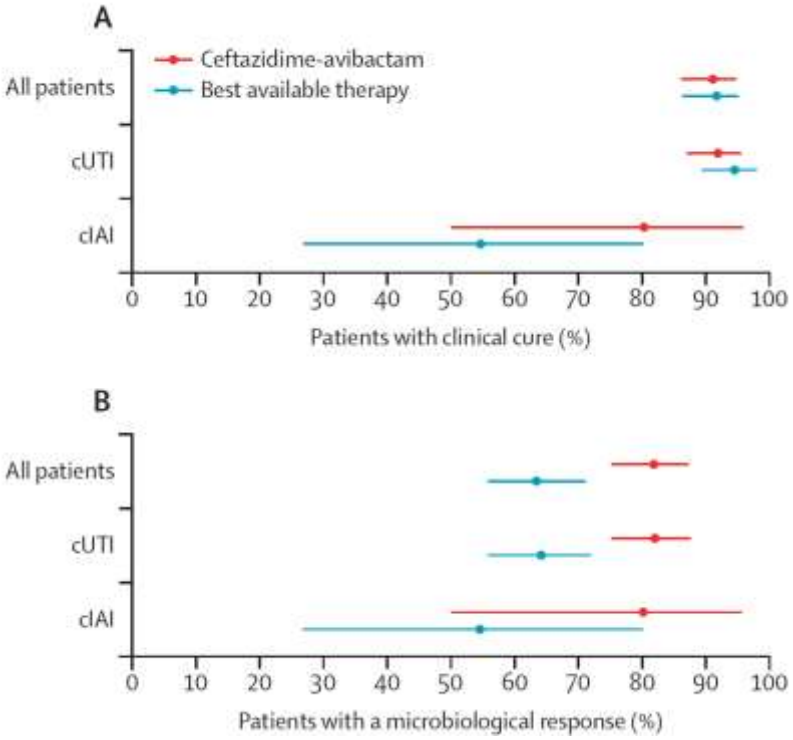
Figure 2. Probability of survival censored at day 14 for patients with extended-spectrum β-lactamase (ESBL)-producing bacteremia in an inverse probability–weighted sample. Solid line represents individuals treated with carbapenems for the entire duration of therapy; dotted line represents individuals treated with piperacillin-tazobactam and converted to carbapenem therapy after ESBL status was known; log-rank test = 0.03.

Tamma PD, et al. Clin Infect Dis 2015.

ESBL: Ceftazidime-avibactam (CAZ-AVI)

Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study

~90% of study: Ceftaz-avi vs. carbapenems for ESBL-E cUTIs



Carmeli Y, et al. Lancet Inf Dis 2016.

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- Her vital signs the morning these results come back (2 days after bacteremia onset) are 37.9, HR 94, BP 96/60. She continues to have GI symptoms. She looks well, but is diaphoretic. The rest of her exam is normal. Her WBC count is < 0.1 cells/µL.

ESBL Treatment: Conclusions

1) Carbapenems remain the treatment of choice for most ESBL infections
2) Cefepime should not be used for ESBL infections outside of the urinary tract
3) Pip-tazo can be considered an alternative to carbapenems for low-inoculum ESBL *E. coli* infections
   - including bacteremia from urine or biliary tract
   - use the 4.5 g q6h dose
4) Randomized clinical trials are need and one is underway!
   - MERINO: Meropenem vs. pip-tazo for ceftriaxone-non-susceptible *Ec* and *Klebsiella* bacteremias
5) Ceftazidime-avibactam is very effective vs. ESBL-E cUTIs and is highly active *in vitro*[1]

[1]Castanheira M, et al. Antimicrob Agents Chemother 2016.

Case #2

- 68 yo man with congestive heart failure is admitted to the CCU for acute pulmonary edema. He receives mechanical ventilation and a central venous catheter is placed. After diuresis and management of his cardiac medications, he is extubated, but 2 days later he develops fever and tachycardia. Blood cultures are collected and he is started on piperacillin-tazobactam. He has no respiratory, abdominal, or urinary symptoms. A chest x-ray is negative. Blood cultures grow *Enterobacter cloacae* with the following susceptibility profile:

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Aztreonam	<=1	S	Levofloxacin	>4	R
Cefepime	<=1	S	Meropenem	<=1	S
Cefazolin	>16	R	Piperacillin-tazobactam	16	S
Cefoxitin	>16	R	TMP-SMX	>2/38	R
Ceftazidime	<=1	S			

- A diagnosis of a central line infection is made and his central venous catheter is removed.

Case 2: Which antibiotic(s) would you choose to treat this bacteremia at this point?

A. Cefepime
B. Ceftriaxone
C. Meropenem
D. Continue piperacillin-tazobactam

AmpC: most often chromosomal

Phenotypic resistance

- Penicillins
- Aminopenicillins
- 1st and 2nd –generation cephalosporins

AmpC enzyme expressed at low levels ("repressed")

Inducer antibacterial agents started

Strong inducers:

- Penicillins, cefazolin
- Cefoxitin
- Carbapenems

Stable vs. ampC

- Beta-lactamase inhibitors (esp. clavulanate): and don't inhibit ampC

Weak inducers:

- Ceftriaxone, ceftazidime, cefepime, aztreonam

Very slowly hydrolyzed vs. ampC

Be cautious about using any of the antibiotics below for SPICE organisms when test susceptible!

Above +

- Ceftriaxone
- Ceftazidime
- Aztreonam
- Piperacillin

Increased transcription of AmpC gene ("derepressed")

Jacoby GA. Clin Microbiol Rev 2009.

AmpC: Concern with ceftriaxone, ceftazidime, aztreonam, maybe pip-tazo

E. cloacae at the start of therapy

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Cefoxitin	>16	R	Piperacillin-tazobactam	16	S
Ceftazidime	<=1	S	TMP-SMX	>2/38	R

E. cloacae 2-4 days into therapy

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Ampicillin/sulbactam	>16	R	Gentamicin	<=1	S
Aztreonam	>16	R	Levofloxacin	>4	R
Cefepime	<=1	S	Meropenem	<=1	S
Cefoxitin	>16	R	Piperacillin-tazobactam	64	I
Ceftazidime	>16	R	TMP-SMX	>2/38	R

AmpC: How often do these antibiotics induce hyperproduction?

- Of all *Enterobacter* infections treated with 3rd-generation cephalosporins -> 10-20% will become resistant on therapy (more likely if bacteremia)[1,2]
- Probably less relevant for "SPI" than "CE"[3]

Organism	% that developed Ceph3 resistance with treatment (all)	% that developed resistance (bacteremia)
S. *marcescens*	0% (0/37)	0% (0/10)
P (*M. morganii*)	0% (0/21)	0% (0/6)
I	N/A	
C. f*reundii*	3% (1/39)	0% (0/8)
E*nterobacter* spp.	8% (10/121)	13% (4/30)

[1]Chow JW, et al. Ann Intern Med 1991.
[2]Kaye KS, et al. Antimicrob Agents Chemother 2001.
[3]Choi SH, et al. Antimicrob Agents Chemother 2008.

Clinical data: Cefepime vs. Meropenem for AmpCs

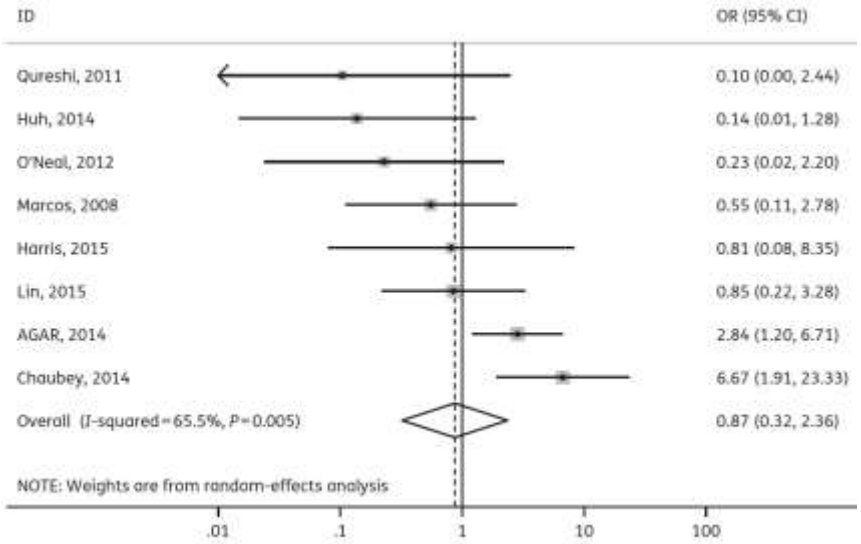
- 72 bacteremias, pneumonias, and intra-abdominal abscesses due to *Enterobacter* and *Serratia* that were AmpC producers by phenotypic testing
  - All ceftriaxone-resistant, but meropenem and cefepime-susceptible
  - 32: meropenem for >=72 hours (including empirical tx)
  - 46: cefepime for >=72 hours (including empirical tx)

Antibiotic	30-day mortality
Cefepime (n=32)	31%
Meropenem (n=32): propensity-score matched	34%

Tamma PD, et al. Clin Infect Dis 2013.

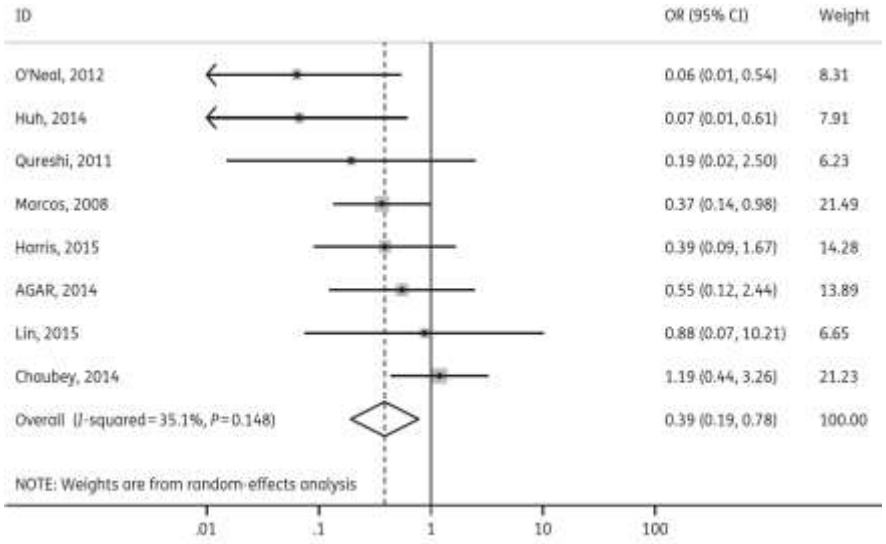
AmpC: What about …

Pip-tazo[1]



Forest plot of unadjusted ORs for mortality in patients given definitive therapy with BLBLIs versus carbapenems.

Fluoroquinolones



Forest plot of unadjusted ORs for mortality in patients given definitive therapy with fluoroquinolones versus carbapenems.

CAUTION:

- Based on very small #s, ?confounding
- Not effective in animal models of plasmid AmpC-*E. coli* infection[2]
- Tazobactam with little AmpC inhibition

[1]Harris PN, et al. J Antimicrob Chemother 2016.
[2]Vimont S, et al. J Antimicrob Chemother 2007.

Case #2

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Cefoxitin	>16	R	TMP/SMX	>2/38	R
Ceftazidime	<=1	S			

- A diagnosis of a central line infection is made and his central venous catheter is removed.

AmpC Treatment: Conclusions

1) Cefoxitin resistance is a great marker for AmpC production and the potential for hyperinduction of AmpC
2) Severe infections due to SPICE organisms in critically ill patients should be treated with a carbapenem
3) Cefepime is a good alternative, particularly for patients who are not critically ill
4) Beware of using cephalosporins other than cefepime (even if initially test susceptible) for these infections as resistance can develop on therapy
5) Role of pip-tazo for these infections unclear
6) Remember fluoroquinolones as possible treatment options

Case #3

- 54 year old kidney transplant recipient with diabetes presents with dysuria, pain over his allograft, and low-grade fever. His blood pressure is normal and is not acutely-ill appearing, but has tenderness over his allograft. His creatinine is 1.7 mg/dL (slightly above baseline) and his urinalysis shows pyuria.
- His blood and urine cultures grow *Klebsiella pneumoniae* with the following susceptibility profile:

Antibiotic	MIC (µg/mL)	Interp.
Ampicillin	>16	R
Ampicillin-sulbactam	>16	R
Aztreonam	>16	R
Cefepime	>16	R
Cefoxitin	>16	R
Ceftazidime	>16	R
Ceftriaxone	>32	R

Antibiotic	MIC (µg/mL)	Interp.
Gentamicin	4	S
Levofloxacin	>4	R
Meropenem	>8	R
Piperacillin-tazobactam	>64	R
Tigecycline	1	S
Colistin	1	“S”
Polymyxin B	1	“S”
TMP-SMX	>2/38	R

Case 3: Which antibiotic(s) would you use for this infection?

A. Polymyxin B or colistin
B. Tigecycline
C. Gentamicin
D. One of the above combined with meropenem
E. Ceftazidime-avibactam
F. Ceftazidime-avibactam + polymyxin B

Carbapenem-resistant Enterobacteriaceae (CRE)

- *Klebsiella pneumoniae* carbapenemase (**KPC**) is by far the most common mechanism for carbapenem resistance for the Enterobacteriaceae in the NE USA (but **CRE ≠ KPC**)
  - Most common with *Klebsiella pneumoniae*
  - KPC is encoded on a **plasmid**
  - Usually test susceptible to poly B/colistin, tigecycline
    - sometimes susceptible to gentamicin, amikacin, doxycycline, and fosfomycin
    - KPC-E usually susceptible to ceftazidime-avibactam (CAZ-AVI)
- CRE bacteremia: **40-50% mortality** rate in the pre-CAZ-AVI era
  - 30-50% mortality rate with combination therapy
- Should we use CAZ-AVI first-line or polymyxin-based regimens?

Munoz-Price LS, et al. Lancet Inf Dis 2013.
Satlin MJ, et al. Clin Infect Dis 2014.
Satlin MJ, et al. Antimicrob Agents Chemother 2017.
Tzouvelekis LS, et al. Clin Microbiol Infect 2014.

Ceftazidime-avibactam (Avycaz™)

- The first approved β-lactam/β-lactamase inhibitor with excellent ***in vitro*** activity vs. ESBL, AmpC, and KPC-producing Enterobacteriaceae[1]
  - Not reliably active vs. metallo-β-lactamases (e.g. NDM) or an improvement vs. *Acinetobacter*
  - Active vs. ~80% of ceftazidime-resistant *Pseudomonas*[2]
  - *Bacteroides* and Gram-positive coverage limited[3]
- FDA-approved in Feb 2015 for complicated intra-abdominal and urinary tract infections
- **Limited clinical data** for use for KPC-*Kp* or bacteremia
- Animal data also limited
- Dose: 2.5g IV over 2h q8h (2 g ceftaz, 0.5 gm avibactam)
- Expensive! (~900/day)

[1]Castanheira M, et al. Antimicrob Agents Chemother 2015.
[2]Sader HS et al. Antimicrob Agents Chemother 2015
[3]Citron DM et al. Antimicrob Agents Chemother 2011.

Clinical data for CAZ-AVI vs. CRE

Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections

Ryan K. Shields,[1,3,4,a] Brian A. Potoski,[1,2,3,a] Ghady Haidar,[1] Binghua Hao,[4] Yohei Doi,[1] Liang Chen,[5] Ellen G. Press,[1] Barry N. Kreiswirth,[6] Cornelius J. Clancy,[1,4,5] and M. Hong Nguyen[1,3,4]

37 patients with CRE infections
- Clinical success: 59%
  - Recurrence in 23% of these
- 30-day mortality: 24%
- Microbiologic failure: 27%
- Development of **resistance**: 8% (3/37)
- AKI rate: 10%

Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by Carbapenem-Resistant Organisms

Elizabeth Temkin,[a] Julian Torre-Cisneros,[i,j] Bojana Beovic,[b] Natividad Benito,[c,d] Maddalena Giannella,[e] Raúl Gilarranz,[f] Cameron Jeremiah,[g] Belén Loeches,[h] Isabel Machuca,[i,j] María José Jiménez-Martín,[k] José Antonio Martínez,[i] Marta Mora-Rillo,[h] Enrique Navas,[m] Michael Osthoff,[n] Juan Carlos Pozo,[o] Juan Carlos Ramos Ramos,[h] Marina Rodriguez,[o] Miguel Sánchez-García,[k] Pierluigi Viale,[p] Michel Wolff,[q,r] Yehuda Carmeli[a,s]

36 patients with CRE infections in a compassionate-use manner:
- Clinical cure: 69%
- In-hospital mortality: 39% (26% infection-related mortality)
- Microbiologic failure: 33%
- Development of **resistance**: not seen

Shields RK, et al. Clin Infect Dis 2016.
Temkin E, et al. Antimicrob Agents Chemother 2017.

Problems with Other CRE-active Agents

Polymyxins

- Nephrotoxicity: 50%[1]
  - Less with poly B
- Difficult to achieve PK-PD targets for pneumonia and for BSI with MICs > 1 µg/mL[2]
  - Use loading doses
  - Colistin is given as inactive drug
- Susceptibility testing available to most labs unreliable[3]
  - Resistance emerging (17% in 2013 CRE BSI study in NY/NJ)[4]

Tigecycline

- Low bloodstream and urine levels[5]
- Increased mortality in RCTs of FDA-approved indications[6]

Aminoglycosides

Sometimes …

- Susceptibilities in 2013 NY/NJ CRE BSI study:[4]
  - Gentamicin: 47%
  - Tobramycin: 12%
  - Amikacin 37%

[1]Rigatto MH, et al. Antimicrob Agents Chemother 2016.
[2]Nation RL, et al. Clin Infect Dis 2016.
[3]Hindler JA, et al. J Clin Microbiol 2013.
[4]Satlin MJ, et al. Antimicrob Agents Chemother 2017.
[5]MacGowan AP, et al. J Antimicrob Chemother 2008.
[6]Prasad P, et al. Clin Infect Dis 2012.

CAZ-AVI

POLYMYXINS

Clinical efficacy

Spectrum of CRE

Toxicity

Resistance

Availability of accurate susceptibility testing

Cost

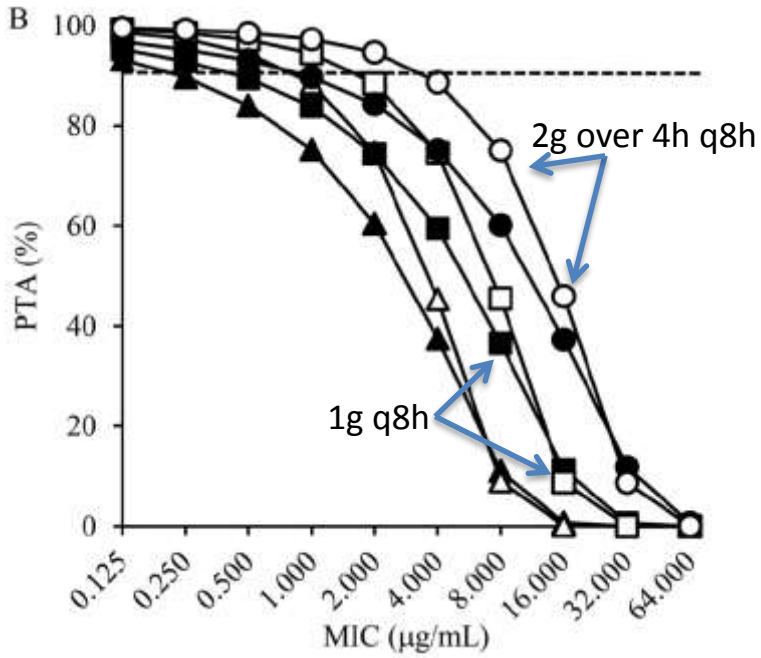
COMBINATION THERAPY?
CAZ-AVI + polymyxins? + meropenem? + aminoglycosides?

CRE: Should we give a carbapenem for a carbapenem-resistant *Kp* infection?

- CLSI breakpoints for meropenem for *Kp*:

MIC	≤1 (S)	2 (I)	≥4 (R)

Chance of getting fT>MIC of 80%[1]



[1]Jaruratanasirikul S, et al. Antimicrob Agents Chemother 2015.

Mortality rates in patients treated with meropenem for carbapenemase-producing *Kp* bacteremia, stratified by meropenem MIC[2,3]

Mero MIC (µg/mL)	30-day mortality
≤8	9/50 (18%)
>8	17/48 (36%)

[2]Tumbarello M, et al. Clin Infect Dis 2012.
[3]Daikos GL, et al. Antimicrob Agents Chemother 2014.

Case #3

- 54 year old renal transplant recipient with diabetes presents with dysuria, pain over his allograft, and a low-grade fever. He has a normal blood pressure and is not acutely-ill appearing, but has tenderness over his allograft. His creatinine is 1.7 mg/dL (slightly above baseline) and his urinalysis shows pyuria.
- His blood and urine cultures grow *Klebsiella pneumoniae* with the following susceptibility profile:

Antibiotic	MIC (µg/mL)	Interp.
Ampicillin	>16	R
Ampicillin-sulbactam	>16	R
Aztreonam	>16	R
Cefepime	>16	R
Cefoxitin	>16	R
Ceftazidime	>16	R
Ceftriaxone	>32	R

Ceftazidime-avibactam: MIC 2 µg/mL

Antibiotic	MIC (µg/mL)	Interp.
Gentamicin	4	S
Levofloxacin	>4	R
Meropenem	>8	R
Piperacillin-tazobactam	>64	R
Tigecycline	1	S
Colistin	1	“S”
Polymyxin B	1	“S”
TMP-SMX	>2/38	R

CRE Treatment: Conclusions

1) Ceftazidime-avibactam and polymyxin-based regimens are the primary treatments (? in combination)
2) Ceftazidime-avibactam is a potential game-changing breakthrough for KPC-producing Enterobacteriaceae BUT:
   - Very limited clinical data, very expensive
   - Not a panacea for all MDR GNs
3) Polymyxin B preferred to colistin
4) Adding a carbapenem to one of these "active" agents is reasonable if the carbapenem MIC is ≤8 μg/mL (maybe even 16) and the 2 g prolonged infusion dosing regimen is used

Case #4

- 73 yo man with coronary artery disease and chronic bronchitis admitted with a VFib arrest. Intubated, resuscitated, and cooled. Taken for cardiac cath, found to have an LAD obstruction. Had angioplasty and stent placed. 5 days into the hospitalization, while still receiving mechanical ventilation, developed fever and increased tracheal secretions and hypoxia. Had tracheal aspirate sent. Gram stain showed moderate WBC and GNRs. Started on vancomycin 1 g IV q12h and pip-tazo 4.5 g q6h. Tracheal aspirate culture grew only *Pseudomonas aeruginosa* with the following susceptibility pattern:

Antibiotic	MIC (µg/mL)	Interp.	Antibiotic	MIC (µg/mL)	Interp.
Amikacin	8	S	Meropenem	2	S
Aztreonam	8	S	Piperacillin-tazobactam	16	S
Cefepime	8	S	Tobramycin	2	S
Ceftazidime	4	S			
Gentamicin	4	S			
Levofloxacin	<=0.5	S			

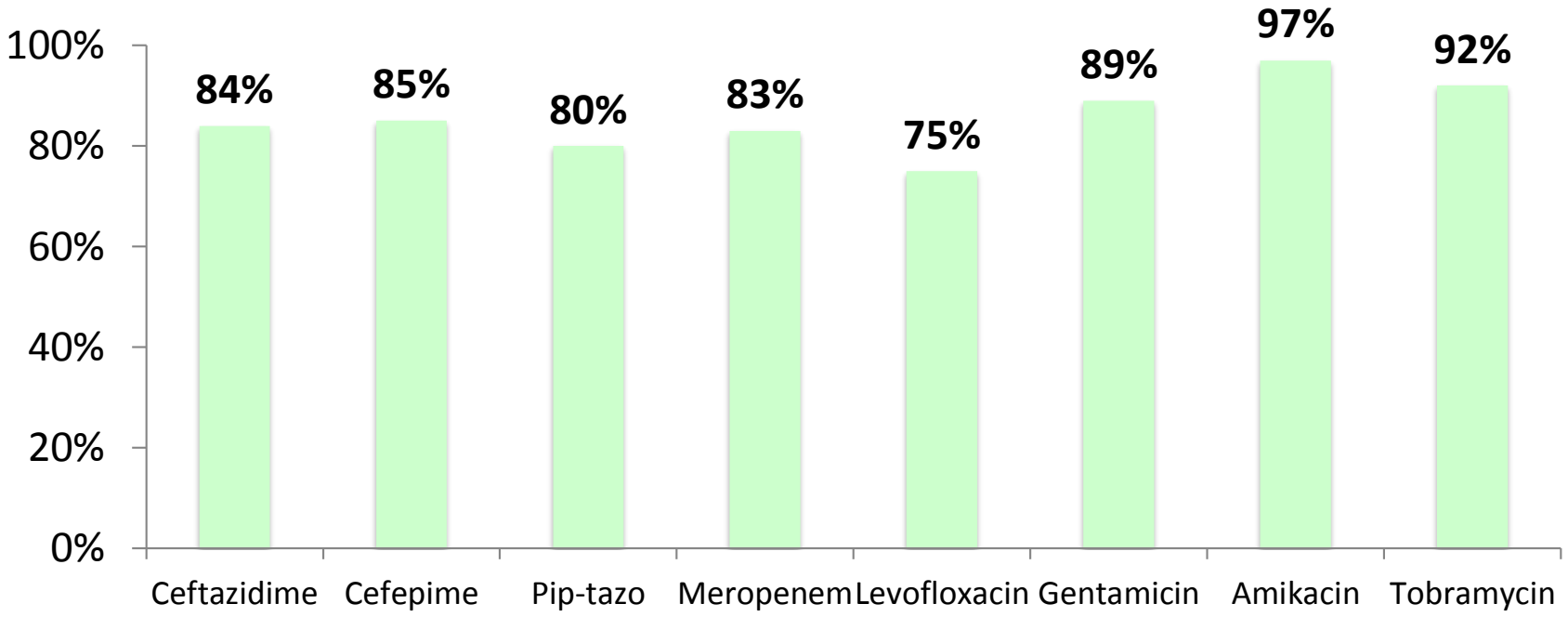
On day 2 (when results available) he is improving on current treatment

Case 4: Which antibiotic(s) and at what dosages would you use for this infection?

A. Pip-tazo: continue 4.5 g (over 30 min) q6h
B. Pip-tazo: change dose to 4.5 g (over 4 h) q8h
C. Pip-tazo (same dose) + aminoglycoside
D. Pip-tazo (same dose) + levofloxacin
E. Change pip-tazo to meropenem, ceftazidime, or cefepime
F. Change pip-tazo to ceftolozane-tazobactam

Pseudomonas aeruginosa

Susceptibility rates: 5328 USA isolates



Empirical therapy in a sick patient (while awaiting susceptibility results)

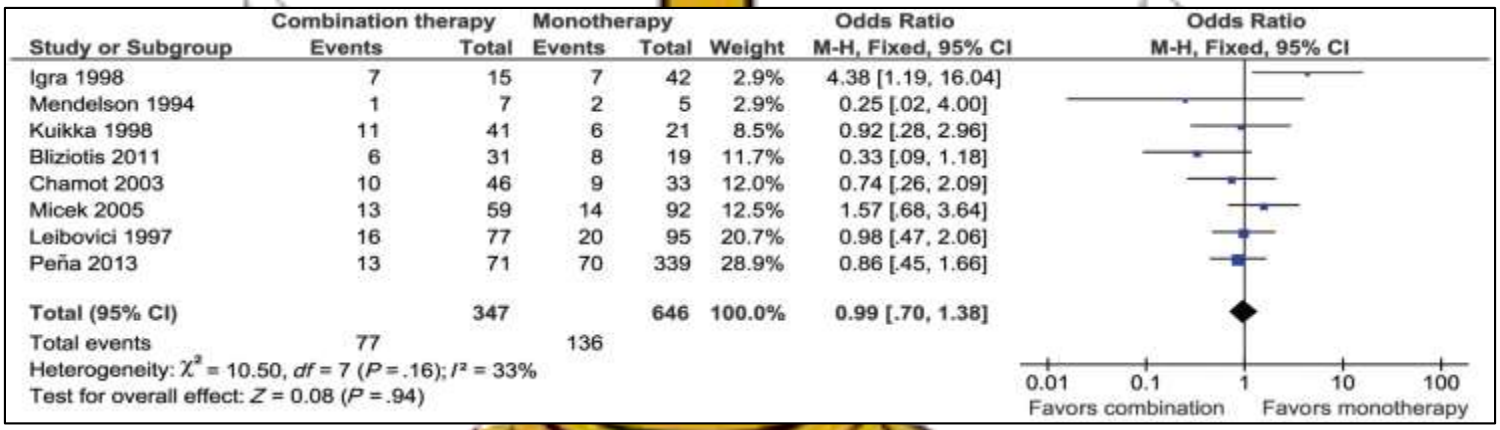
- Reasonable to give β-lactam + aminoglycoside OR fluoroquinolone

Sader HS, et al. Diagn Microbiol Infect Dis 2015.

Pseudomonas aeruginosa:
Rationale for combination definitive therapy

No quality randomized controlled trials

But, most studies do not find a benefit



Study or Subgroup	Combination therapy Events	Total	Monotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Igra 1998	7	15	7	42	2.9%	4.38 [1.19, 16.04]
Mendelson 1994	1	7	2	5	2.9%	0.25 [.02, 4.00]
Kuikka 1998	11	41	6	21	8.5%	0.92 [.28, 2.96]
Bliziotis 2011	6	31	8	19	11.7%	0.33 [.09, 1.18]
Chamot 2003	10	46	9	33	12.0%	0.74 [.26, 2.09]
Micek 2005	13	59	14	92	12.5%	1.57 [.68, 3.64]
Leibovici 1997	16	77	20	95	20.7%	0.98 [.47, 2.06]
Peña 2013	13	71	70	339	28.9%	0.86 [.45, 1.66]
Total (95% CI)		**347**		**646**	**100.0%**	**0.99 [.70, 1.38]**
Total events	77		136			

Heterogeneity: $\chi^2 = 10.50$, $df = 7$ ($P = .16$); $I^2 = 33\%$

Test for overall effect: $Z = 0.08$ ($P = .94$)

Synergy

Increased adverse effects

Prevention of the emergence of resistance

Cost

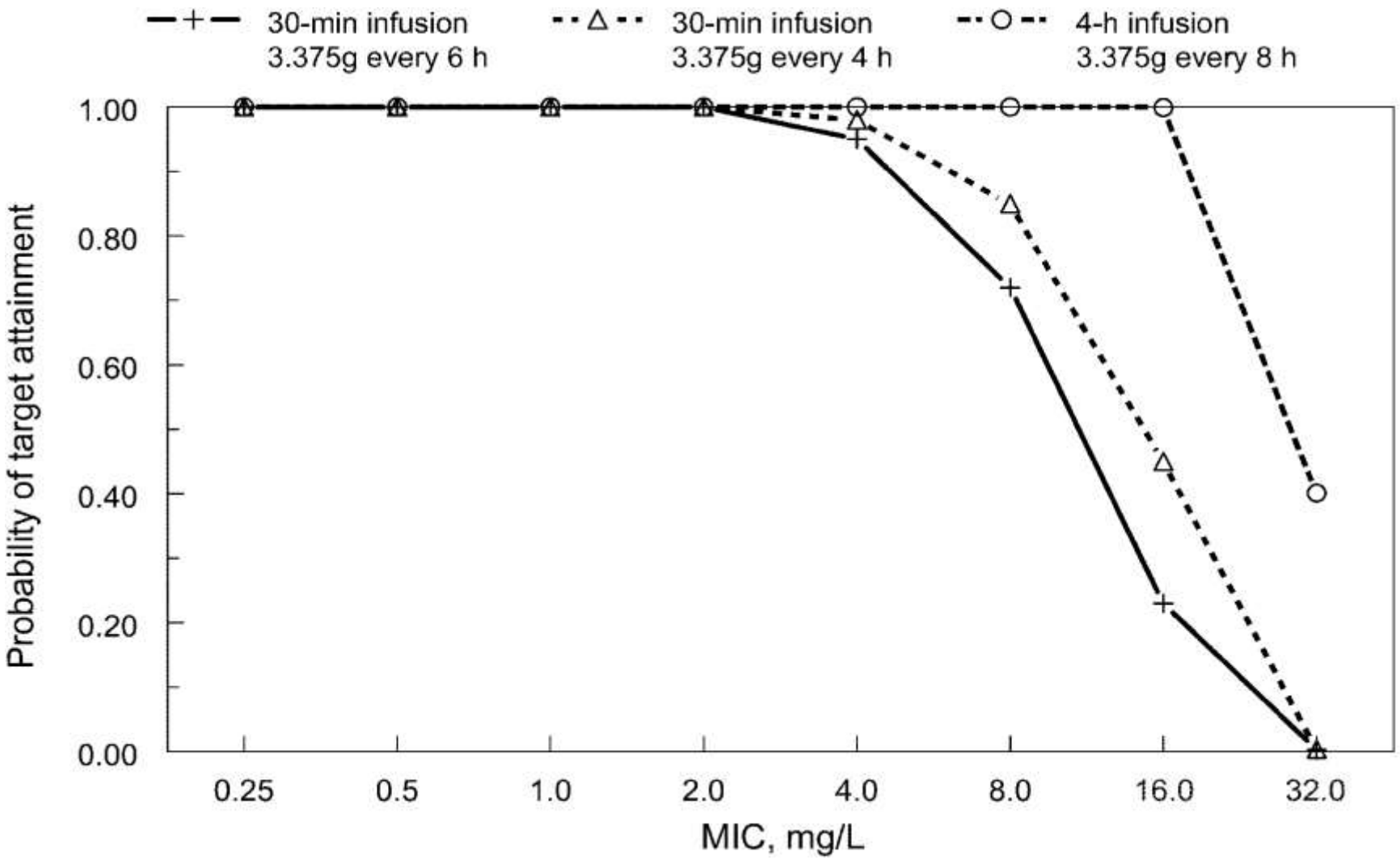
Paul M, et al. Clin Infect Dis 2013.

Pseudomonas aeruginosa
Emergence of resistance while on therapy

- Resistance emerges on therapy in at least 10% of cases[1]
  - Highest with carbapenems and pneumonia[1]
- Solutions?
  1) Use higher doses: pip-tazo (4.5q6h) or cefepime (2q8h)
  2) Add an aminoglycoside or a FQ to the β-lactam (some supportive *in vitro* and animal models)[2-4]
  3) **Prolonged infusion** of β-lactam (eg: over 3-4 h vs. 30 min)
     - More likely to achieve PK target of keeping the concentration of β-lactam > MIC for at least 50% of dosing interval[4]
     - 2 observational studies of prolonged-infusion pip-tazo and cefepime showed decreased mortality for serious *Pa* infections[5-6]

[1]Carmeli Y, et al. Antimicrob Agents Chemother 1999.
[2]Drusano GL, et al. Antimicrob Agents Chemother 2012.
[3]Louie A, et al. Antimicrob Agents Chemother 2010.
[4]Michea-Hamzehpour M, et al. Antimicrob Agents Chemother 1987.
[5]Lodise TP, et al. Clin Infect Dis 2007.
[6]Bauer KA, et al. Antimicrob Agents Chemother 2013.

Probability of achieving PK-PD target with different pip-tazo dosing strategies for *P. aeruginosa* by MICs



Lodise TP, et al. Clin Infect Dis 2007.

Pseudomonas aeruginosa

Clinical Impact of prolonged infusions of pip-tazo

-Before (intermittent infusion): 2000-2002: 3.375 gm q4h over 30 min
-After (extended infusion): 2002-2004: 3.375 gm q8h over 4 hours

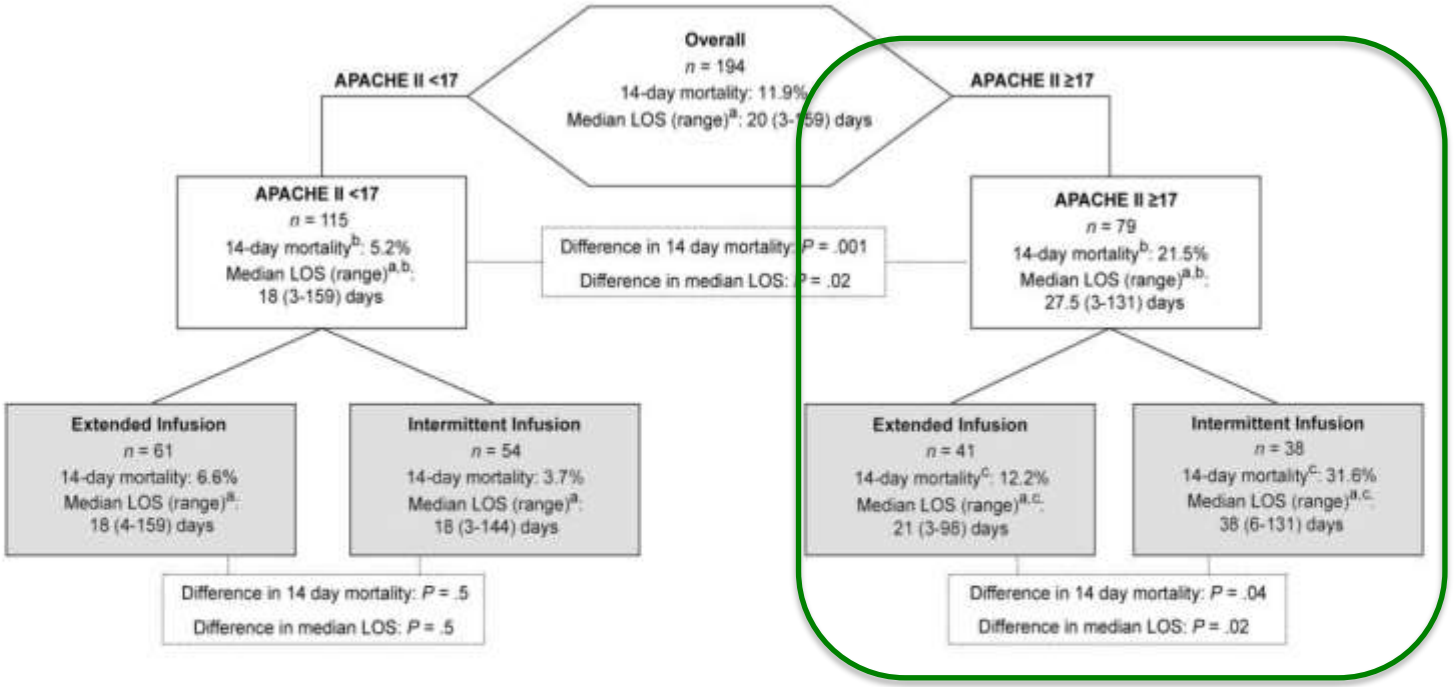


Figure 2. Comparison of outcomes of patients with APACHE II scores ⩾17 and patients with APACHE II scores <17 (the Classification and Regression Tree [CART]–derived breakpoint) who received either an extended infusion of piperacillin-tazobactam or an intermittent infusion of piperacillin-tazobactam. LOS, length of stay. [a]Excludes patients that died within 14 days of collection of *P. aeruginosa*–positive culture sample. [b]Comparison between patients with an APACHE II score <17 and patients with an APACHE II score ⩽17 was $P < .05$. [c]Comparison between the extended group and the intermittent infusion group was $P < .05$.

Lodise TP, et al. Clin Infect Dis 2007.

Pseudomonas aeruginosa

Clinical Impact of prolonged infusions of cefepime

Both groups: 2g q8h

TABLE 2 Comparisonof clinical and economic outcomes f… remia a… epime intermittent-or extended-infusion treatment

Over 30 mins

Over 4 h

Clinical or economic outcome	Infusion treatment[a] Intermittent (n = 54)	Extended (n = 33)	P^b
Mortality	11 (20)	1 (3)	0.03
LOS			
Hospital	14.5 (6–30)	11 (7–20)	0.36
Infection related	12 (6–21)	10 (6–16)	0.45
ICU	18.5 (5.5–32.5)	8 (4–20)	0.04
Duration (days) of mechanical ventilation	14.5 (5–30)	10.5 (8–18)	0.42
Cost (US$)			
Total hospital costs	51,231 (17,558–107,031)	28,048 (13,866–68,991)	0.13
Infection-related hospital costs	15,322 (8,343–27,337)	13,736 (10,800–23,312)	0.78

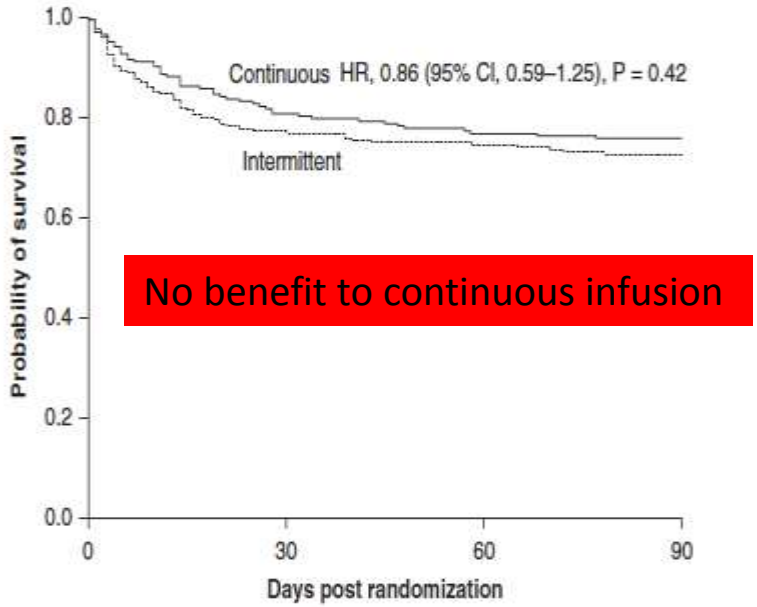
TABLE 3 Exactlogistic regression model for the occurrence of mortality

Variable	OR (95% CI)	P
Infusion type	0.06 (0.001–0.64)	0.01
ICU admission at time of culture collection	8.88 (1.45–100.85)	0.01
APACHE II score	1.13 (1.03–1.27)	0.01

Bauer KA, et al. Antimicrob Agents Chemother 2013.

Clinical Trials of Prolonged-Infusion β-lactams for *P. aeruginosa*

RCT: **Continuous**-infusion β-lactam **vs. intermittent** infusion in 432 ICU patients with severe sepsis (blinded).



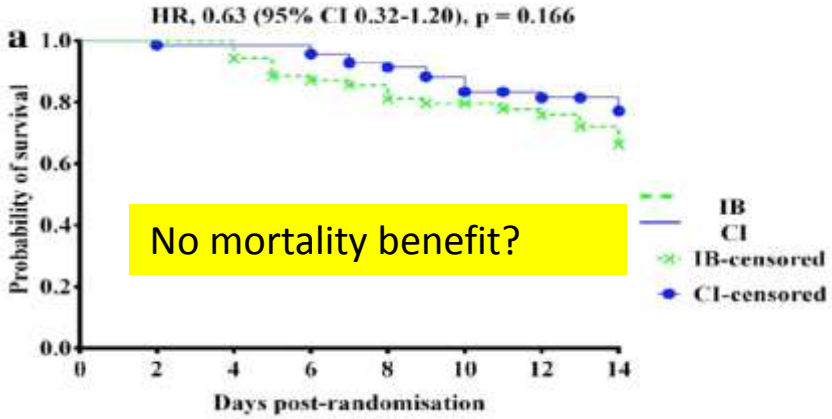
No benefit to continuous infusion

Figure 3. Kaplan-Meier plot for modified intention-to-treat population. CI = confidence interval; HR = hazard ratio.

- Only 14% of patients with a Gram-negative infection documented
  - Even smaller % with *P. aeruginosa*

Dulhunty JM, et al. Am J Resp Crit Care Med 2015.

RCT: **Continuous**-infusion β-lactam **vs. intermittent** infusion in 140 ICU patients with severe sepsis (open-label).



No mortality benefit?

Clinical cure overall: 56% vs. 34% (*P*=0.01)

- Pneumonia: 59% vs. 33%
- 35% of patients with *P. aeruginosa* or *A. baumannii* infections: 52% vs. 25% (*P*=0.05)

Abdul-Aziz MH, et al. Intensive Care Med 2016.

Treatment options for MDR *Pa* resistant to all β-lactams

- Polymyxins and aminoglycosides
  - Not effective as monotherapy for *Pa* bacteremia in neutropenic patients

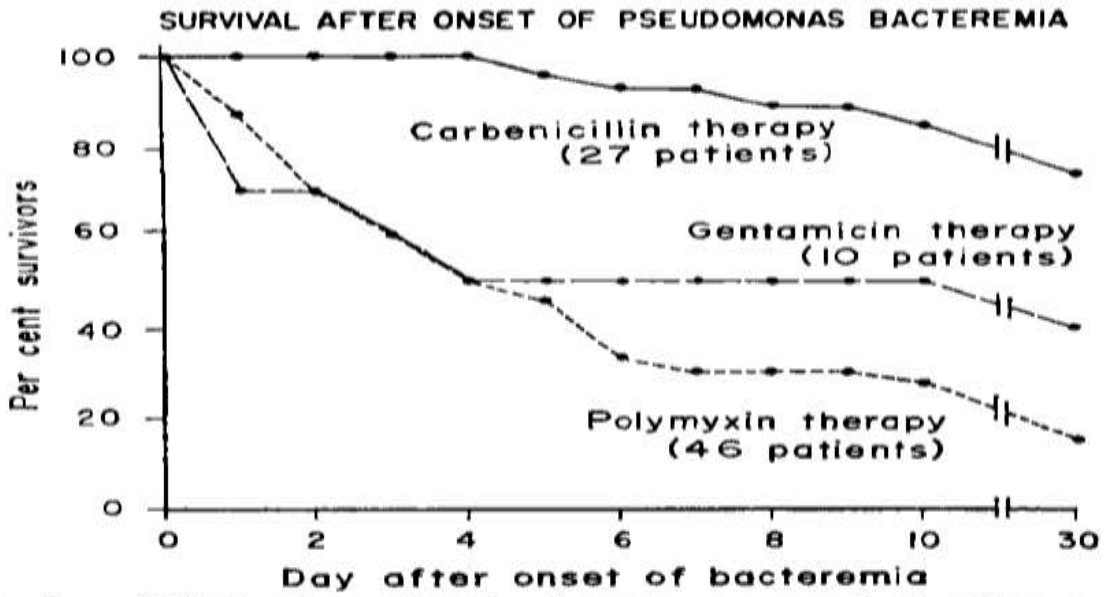


Fig. 5. Effect of antibiotic therapy on survival after onset of Pseudomonas septicemia in cancer patients.

Bodey GP, et al. Eur J Cancer 1973.

Ceftolozane-tazobactam (Zerbaxa™)

- Ceftolozane is a new cephalosporin that is similar to ceftazidime, but less susceptible to AmpC hydrolysis
  - Active against 70% of *Pa* isolates that are non-susceptible to ceftazidime, pip-tazo, and meropenem[1]
  - Tazobactam gives it activity against most ESBLs[1]
  - Gram-positive coverage similar to ceftazidime and *Bacteroides* coverage not reliable[2]
- FDA-approved in Dec 2014 for complicated intra-abdominal (with metronidazole) and urinary tract infections
- **No clinical data** for use for MDR *Pa* OR bacteremia/pneumonia OR neutropenic patients
  - Phase 3 clinical trial for pneumonia ongoing: using dose of 3 gm IV q8h (FDA-approved dose 1.5 gm IV q8h)
  - I recommend this dose for MDR *Pa* bacteremia or pneumonia
- Not as expensive as ceftazidime-avibactam (~$250 per day)

[1]Farrell DJ, et al. Antimicrob Agents Chemother 2013.
[2]Snydman DR, et al. Antimicrob Agents Chemother 2014.

In vitro data: Ceftolozane for MDR *Pa*

TABLE 3 Cumulative MIC distributions of ceftolozane/tazobactam against *P. aeruginosa* by resistance phenotype

P. aeruginosa resistance status (no. of isolates tested)[a]	No. of isolates (cumulative %) inhibited at ceftolozane/tazobactam MIC (μg/ml) of:												MIC_{50}	MIC_{90}
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
All isolates (1,971)	0 (0.0)	2 (0.1)	3 (0.3)	72 (3.9)	958 (52.5)	594 (82.6)	152 (90.4)	113 (96.1)	47 (98.5)	10 (99.0)	4 (99.2)	16 (100.0)	0.5	2
MDR (310)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	9 (3.5)	79 (29.0)	81 (55.2)	74 (79.0)	35 (90.3)	10 (93.5)	4 (94.8)	16 (100.0)	2	8
XDR (175)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	28 (17.1)	50 (45.7)	44 (70.9)	26 (85.7)	8 (90.3)	2 (91.4)	15 (100.0)	4	16
PDR (1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	>32	>32
CAZ-S (1,633)	0 (0.0)	2 (0.1)	3 (0.3)	72 (4.7)	957 (63.3)	542 (96.5)	53 (99.8)	4 (100.0)					0.5	1
CAZ-NS (338)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	52 (15.7)	99 (45.0)	109 (77.2)	47 (91.1)	10 (94.1)	4 (95.3)	16 (100.0)	4	8
MEM-S (1,583)	0 (0.0)	2 (0.1)	3 (0.3)	69 (4.7)	899 (61.5)	450 (89.9)	80 (94.9)	60 (98.7)	18 (99.9)	1 (99.9)	0 (99.9)	1 (100.0)	0.5	2
MEM-NS (388)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	59 (16.0)	144 (53.1)	72 (71.6)	53 (85.3)	29 (92.8)	9 (95.1)	4 (96.1)	15 (100.0)	1	8
CAZ-NS, MEM-NS (183)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	24 (13.1)	50 (40.4)	52 (68.9)	29 (84.7)	9 (89.6)	4 (91.8)	15 (100.0)	4	32
P/T-S (1,513)	0 (0.0)	2 (0.1)	3 (0.3)	71 (5.0)	931 (66.6)	459 (96.9)	39 (99.5)	4 (99.7)	2 (99.9)	1 (99.9)	0 (99.9)	1 (100.0)	0.5	1
P/T-NS (458)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	27 (6.1)	135 (35.6)	113 (60.3)	109 (84.1)	45 (93.9)	9 (95.9)	4 (96.7)	15 (100.0)	2	8
CAZ-NS, MEM-NS, P/T-NS (175)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (12.6)	47 (39.4)	51 (68.6)	29 (85.1)	8 (89.7)	4 (92.0)	14 (100.0)	4	32
Cefepime-S (1,624)	0 (0.0)	2 (0.1)	3 (0.3)	71 (4.7)	955 (63.5)	534 (96.4)	49 (99.4)	9 (99.9)	0 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)	0.5	1
Cefepime-NS (347)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (1.2)	60 (18.4)	103 (48.1)	104 (78.1)	47 (91.6)	10 (94.5)	4 (95.7)	15 (100.0)	4	8
Levofloxacin-S (1,477)	0 (0.0)	2 (0.1)	3 (0.3)	62 (4.5)	866 (63.2)	403 (90.5)	69 (95.1)	51 (98.6)	17 (99.7)	0 (99.7)	2 (99.9)	2 (100.0)	0.5	1
Levofloxacin-NS (494)	0 (0.0)	0 (0.0)	0 (0.0)	10 (2.0)	92 (20.7)	191 (59.3)	83 (76.1)	62 (88.7)	30 (94.7)	10 (96.8)	2 (97.2)	14 (100.0)	1	8
Gentamicin-S (1,758)	0 (0.0)	2 (0.1)	3 (0.3)	69 (4.2)	934 (57.3)	513 (86.5)	103 (92.4)	87 (97.3)	34 (99.3)	3 (99.4)	4 (99.7)	6 (100.0)	0.5	2
Gentamicin-NS (213)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)	24 (12.7)	81 (50.7)	49 (73.7)	26 (85.9)	13 (92.0)	7 (95.3)	0 (95.3)	10 (100.0)	1	8

[a] Abbreviations: MDR, multidrug resistant; XDR, extensively drug resistant; PDR, pan-drug resistant; NS, nonsusceptible; R, resistant; S, susceptible; CAZ, ceftazidime; MEM, meropenem; P/T, piperacillin-tazobactam.

Farrell DJ, et al. Antimicrob Agents Chemother 2013.

P. aeruginosa Treatment: Conclusions

1) 15-20% of *P. aeruginosa* are resistant to a given anti-pseudomonal β-lactam ➔ consider combination therapy while await susceptibilities in sick patients
2) Once susceptibility data return, no clinical data to support given 2 agents that are active *in vitro*
   - However … resistance frequently develops on monotherapy, especially with carbapenems for *P. aeruginosa* pneumonia
3) Prolonged infusion a reasonable strategy for *P. aeruginosa* infections
4) Ceftolozane-tazobactam a promising option for β-lactam-resistant *P. aeruginosa* infections, but limited clinical data


ANY
QUESTIONS
?